UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: August 5, 2014
TXR #: 0056942

SUBJECT: **Fenazaquin:** Summary of Hazard and Science Policy Council (HASPOC) Meeting of April 10, 2014: Recommendations on the need for subchronic inhalation, subchronic dermal, rabbit developmental, and neurotoxicity studies.

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MEETING ATTENDEES:

HASPOC Members: Anna Lowit, Elissa Reaves, Elizabeth Mendez, Jeff Dawson, John Kough, Jonathan Chen, Michael Metzger, P.V. Shah, Ray Kent, Julie Van Alstine, Uma Habiba, Jonathan Leshin, Monique Perron

Presenters: Vincent Chen, Kristin Rury, Cassi Walls

Other Attendees: Margarita Collantes, Jaime D'Agostino, Matt Lloyd, Christina Schwartz, Doug Dotson, Matt Crowley.

I. PURPOSE OF MEETING:

Risk Assessment Branch III (RAB III) is preparing a human-health risk assessment for fenazaquin for use on various agricultural crops. The Hazard and Science Policy Council (HASPOC) and Toxicology Science Advisory Council (TOXSAC) have met to discuss toxicology needs for fenazaquin multiple times. Most recently on February 28, 2013, the HASPOC discussed the need for an acute neurotoxicity study (ACN), a subchronic neurotoxicity study, a subchronic dermal toxicity study, a rabbit developmental toxicity study, and a subchronic inhalation toxicity study (TXR#0056595). At that time, the HASPOC concluded that the following studies were needed: (1) a subchronic dermal toxicity study or dermal penetration study; (2) a rabbit developmental toxicity study; (3) an ACN study; (4) a subchronic neurotoxicity study (pending the results of the ACN study); and (5) a subchronic inhalation toxicity study. The HASPOC also recommended that the registrant (Gowan) submit protocols for agency review prior to the initiation of any of the previously mentioned studies. The HASPOC also recommended that a 10X database uncertainty factor should be applied to all routes and durations of exposure for risk assessment.

Recently, the risk assessment team met with the registrant to discuss the toxicological database's deficiencies. Based on this discussion, in addition to revised exposure calculations, the team requested the HASPOC to meet on April 10, 2014 to revisit the need for these studies.

II. SUMMARY OF USE PROFILE & PREVIOUS RISK ASSESSMENT:

Fenazaquin, 3-[2-[4-(1,1-dimethylethyl) phenyl] ethoxy] quinazoline, is a quinazoline-derived insecticide used to control mites and whiteflies. Fenazaquin's pesticidal mode of action is through inhibition of the mitochondrial electron transport at the Complex I site (NADH-ubiquinone reductase). There are no mammalian molecular data to specifically show this mode of action in test animals. However, chemicals disrupting mitochondrial respiration will reduce ATP (readily available chemical energy); a hallmark of this disruption is generalized toxicity, such as decreased body weight, food consumption, and food efficiency. Fenazaquin's mammalian toxicity profile is consistent with this pattern.

Fenazaquin is currently registered as an emulsifiable concentrate (EC, 18.79% ai) for use on ornamental plants outside and in greenhouses, Christmas tree plantations, and non-bearing fruit and nut trees. Fenazaquin has been proposed for use on the following agricultural crops: alfalfa grown for seed; avocado; Beans, Dry (Crop Subgroup 6C); Beans, Succulent (Crop Subgroup 6A and Crop Subgroup 6B); Berry (Crop Subgroup 13-07A and Crop Subgroup 13-07B); Citrus group (Crop Group 10-10); Corn, Field; Corn, Sweet, Cotton; Cucurbits (Crop Group 9); Fruiting Vegetables in fields and greenhouses (Crop Group 8); Grapes; Hops; Mint; Pome Fruit

(Crop Group 11-10); Stone Fruit (Crop Group 12); Strawberries, and Tree Nuts (Crop Group 14). The labels require occupational handlers to wear long sleeved shirts, long pants, chemical resistant gloves, shoes, and socks; for mixing/loading/applying using a high pressure handwand, coveralls are also required.

Fenazaquin may be applied to the proposed and registered use sites with handheld, ground, and airblast equipment. The fenazaquin labels allow one application per "cropping"; therefore, exposure to fenazaquin is expected to only be short-term in duration for occupational handlers in outdoor settings. However, intermediate-term exposure was also assessed for greenhouse grown ornamentals since there is potential for repeated exposure in greenhouses and crops can be grown throughout the year for multiple "croppings." Fenazaquin is intended for occupational use only, but it is also currently registered for use on several residential/non-agricultural use sites and is not a restricted use pesticide. Therefore, residential handler and residential post-application assessments were conducted using the revised Residential Standard Operating Procedures (SOPs).

In the most recent risk assessment (J. Arthur *et al.*, D373139, 01/14/2010), the acute point of departure (POD) [no observed adverse effect level (NOAEL) =10 mg/kg/day] was based on two studies: the acute oral toxicity study (870.1100) and maternal effects in the rat developmental toxicity study. In the acute oral study, the lowest observed adverse effect level (LOAEL) of 50 mg/kg/day was based on hunched posture, straub tail, hypoactivity, and soft stools. In the rat developmental toxicity study, the LOAEL of 40 mg/kg/day was based on decreased body weight gain, food intake, and food efficiency [as early as gestation day (GD) 6-9] in dams. The chronic dietary exposure was assessed using a NOAEL of 5 mg/kg/day based on excessive salivation and decreased body weight/body weight gain and food intake seen at the LOAEL of 25 mg/kg/day in the rat two-generation toxicity study.

Short-term dermal and inhalation exposures were assessed using a NOAEL of 10 mg/kg/day based on decreased body weight, body weight gain, food intake, and food efficiency seen at the LOAEL of 40 mg/kg/day in the rat developmental toxicity study. Intermediate-term dermal and inhalation exposures were assessed using a NOAEL of 5 mg/kg/day based on decreased body weight, body weight gain, food consumption, and efficiency seen at the LOAEL of 15 mg/kg/day in a 90-day rat feeding study. Similar effects were seen in 90-day and chronic feeding studies in rats with comparable LOAELs. Since the 2010 risk assessment, a subchronic dermal toxicity study has been submitted (see below).

There is no concern for increased quantitative or qualitative susceptibility of the young following *in utero* (rats and rabbits) and pre-and post-natal exposure (rats) to fenazaquin. The Food Quality Protection Act (FQPA) safety factor has been reduced to 1X.

In the 2010 risk assessment, acute dietary exposure and risks were estimated using the DEEM-FCID Model for the registered uses and resulted in risk estimates that utilized 24% acute population adjusted dose (aPAD) for the highest exposed population subgroup, children 1-2 years of age. Chronic dietary exposure and risk estimates utilized 13% of the chronic population adjusted dose (cPAD) for children 1-2 years of age, the highest exposed population subgroup.

Residential handler short-term inhalation margins of exposure (MOEs) ranged from 380,000 to 3,000,000. Occupational short-term handler inhalation MOEs ranged from 2,200 (mixing/loading for greenhouse application with a mechanically pressurized handgun) to 220,000 at baseline PPE (no respirator). Intermediate-term occupational handler exposure was assessed for the proposed occupational use of fenazaquin on fruiting vegetables in greenhouses. The intermediate-term baseline inhalation MOEs ranged from 1,100 (mixing/loading/applying using a mechanically pressurized handgun) to 110,000.

III. STUDY WAIVER REQUESTS:

a. Subchronic Inhalation Toxicity

Previously, the Office of Pesticide Programs (OPP) used a set of criteria to determine whether or not an inhalation study could be waived. These criteria considered the scientific information available for the chemical, including its: (1) degree of irritation and corrosivity; 2) volatility; 3) aerosol particle size; and 4) Acute Toxicity Category and extrapolated MOEs (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PODs were protective of potential inhalation toxicity varied. In many cases, the oral POD was protective, but in some cases the inhalation PODs were significantly more protective. Currently, OPP uses a weight of evidence (WOE) approach that builds upon OPP's experience using the criteria listed above and conclusions from the 2009 SAP. As approaches for route-to-route extrapolation continue to evolve and improve, OPP may incorporate additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of inhalation exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. OPP's interim WOE approach considers:

- **Physical Chemical Properties:** Vapor pressure and Henry's law constant are key considerations with respect to the volatilization after sprays have settled. Fenazaquin has a low vapor pressure (1.43×10^{-7} mmHg) at 25°C. However, low vapor pressure does not preclude exposure to aerosolized droplets or particles/dust.

- **Use Pattern and Exposure Scenarios:** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. Airblast and aerial applications are more likely to lead to higher occupational handler inhalation exposure, particularly to droplets, and may also contribute to spray drift. In the case of fenazaquin, handwand applications resulted in the highest inhalation exposure (MOE = 1,100).

- **Margins of Exposure:** The MOE estimates for inhalation scenarios were calculated using an oral toxicity study and should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern (LOC) as a benchmark for granting waiver requests. The

2009 analysis suggests this approach is appropriate for most pesticides, but not all. Using this interim WOE approach, MOEs from 10-100 times greater than the LOC will be considered in combination with other factors discussed here. Residential exposure to fenazaquin resulted in MOEs ranging from 380,000 to 3,000,000. Occupational exposure resulted in MOEs ranging from 1,100 to 220,000.

- **Toxicological Effects:** Fenazaquin is classified as Toxicity Category II for acute oral toxicity and Toxicity Category III for acute inhalation toxicity. Fenazaquin is not a dermal irritant, but was classified as a dermal sensitizer. The effects seen consistently throughout the database include decreased body weight, body weight gain, and food consumption. There is no evidence of developmental or reproductive toxicity. Fenazaquin is classified as "not likely to be carcinogenic to humans."

Based on a WOE approach, HASPOC concludes that a subchronic inhalation toxicity study is not needed for fenazaquin at this time. This approach considered all of the available hazard and exposure information for fenazaquin, including: 1) its physical/chemical properties, including its low vapor pressure (1.43×10^{-7} mmHg); (2) its toxicological profile, including its low acute inhalation toxicity (Toxicity Category III); and (3) the use of an oral POD for assessing short- and intermediate-term exposure scenarios (i.e. a conservative approach) results in screening-level MOEs that are >1,000.

b. Subchronic Dermal Toxicity

As noted above, currently, the short- and intermediate-term dermal exposures are assessed using PODs derived from oral studies with a 100% dermal absorption factor (DAF). Since the most recent risk assessment in 2010, a subchronic dermal toxicity study in the rabbit has been submitted where no systemic toxicity was observed up to 1000 mg/kg/day, suggesting no dermal hazard for fenazaquin.

The new dermal toxicity study in rabbits has some deficiencies with respect to the guideline requirements and previously the HASPOC indicated that additional dermal data (either another subchronic dermal toxicity study or a dermal absorption study) are needed to more accurately assess dermal risk to fenazaquin. However, following discussions between the risk assessment team and the registrant, the HASPOC reconsidered the need for additional dermal toxicology data.

The deficiencies noted in the new dermal toxicity study include: a) only 5 animals/sex/dose group were evaluated (the guideline recommends 10 animals/sex/dose group); b) neurological evaluations were not conducted; c) hematology did not include blood clotting measurements; d) clinical chemistry did not include total cholesterol; e) organ weight data did not include the brain, spleen, epididymides, uterus, and thymus; and f) histopathology was not performed on the parathyroids, pharynx, larynx, nose, epididymides, and seminal vesicles. In oral toxicity studies with fenazaquin, effects of concern relate to mortality (acute) and non-specific endpoints, such as decreased body weight and food consumption, that are often associated with mitochondrial inhibitors. The lack of the previously noted measurements are not expected to be highly sensitive metrics for fenazaquin and, therefore, the lack of these measurements does not reduce

the overall confidence in the conclusions of the dermal toxicity study. Additionally, given there was ***no*** systemic toxicity observed up to the limit dose and target organs were evaluated in this study, substantive new information will not be gained by repeating the study with more animals. Furthermore, the use of an oral POD with a 100% DAF is highly conservative. Fenazaquin has a relatively high partition coefficient ($\log K_{OW} = 5.7$). Also, in a rat *in vitro* study, the DAF was estimated at approximately 7%. Although HED would not quantitatively use this *in vitro* value for risk assessment, it does show that fenazaquin is expected to have relatively low dermal absorption especially since rat skin is approximately 3-10 times more permeable than human skin.

Based on a WOE approach, HASPOC concludes that a subchronic dermal toxicity study is not needed for fenazaquin at this time. Conducting an additional dermal toxicity study would not impact the dermal POD. Despite the noted deficiencies, the rabbit subchronic dermal toxicity study is sufficient for use in assessing the dermal risk of fenazaquin.

c. Rabbit Developmental Toxicity (Guideline 870.3700):

Previously, the HASPOC indicated that a rabbit developmental toxicity study was needed. The existing study (MRID 45029912) was unacceptable because: 1) the treatment duration was abbreviated [dosing occurred from gestation day (GD) 6-18] missing a potential window of developmental susceptibility (during the critical period of organogenesis); and 2) the highest dose tested was not adequate to assess the potential developmental toxicity. The team requested that the HASPOC reconsider the need for a new rabbit developmental toxicity study.

In 1998, the guideline for rabbit developmental toxicity studies was changed. Dosing duration in the old guideline was revised from GD 6-18 to a longer dosing period, GD 6-28. The fenazaquin rabbit developmental toxicity study was conducted in 1990, prior to the change in the guideline, but it was submitted to the agency in 2006. In 2000, the agency generally no longer accepted new submissions of the old rabbit developmental guideline study. However, the agency did accept this specific study for fenazaquin until recently. With respect to the need for a new study, there are two key considerations: 1) dose levels used in the study; and 2) uncertainty/confidence associated with the findings of the older guideline with fewer days of dosing.

i. *Dosing adequacy:* In the developmental rabbit study, pregnant rabbits were dosed by gavage at 0, 3, 13, or 60 mg/kg bw/day. No treatment-related clinical signs were observed in does administered any dose of the test material. Maternal body weight, weight gain, and net weight gain of does administered the test material were similar to those of the control group. There was no systemic toxicity observed at the highest dose tested (60 mg/kg/day). However, based on studies in other species (rat, dog, hamster), a dose of 60 mg/kg/day is considered to be relatively high for fenazaquin suggesting that rabbits may be less sensitive than other species.

   There were a relatively high number (six) of does in the 60 mg/kg/day group that died or were humanely sacrificed due to gavage accidents, broken backs, and/or abortion of their litters. As a result, the HASPOC does not consider the results for the 60 mg/kg/day dose group to be reliable given the suggestions of poor animal handling and the insufficient number of litters to assess fenazaquin exposure on the developing

fetus due to the mortalities/sacrifices at this dose. However, the data for the 3 and 13 mg/kg/day groups are consider reliable and no adverse maternal findings were observed at these doses. With respect to maternal animals, repeating the study at doses higher than 13 mg/kg/day would not yield a lower POD since no effects were seen up to 13 mg/kg/day and the current PODs are based on effects seen in the rat, a more sensitive species, at lower doses.

ii. *Uncertainty/confidence associated with the findings of the older guideline with fewer days of dosing*: In the fenazaquin rabbit developmental toxicity study, the LOAEL was not established. The NOAEL was the highest dose tested (60 mg/kg/day). No treatment-related effects were observed on the number of live fetuses/litter, number of resorptions/litter (early, late, and total), fetal weight (male, female, or combined), percent male fetuses/litter, or incidence of malformations/variations. Three litters were aborted between GD 23 and 26, one from the 13 mg/kg/day group and two from the 60 mg/kg/day group. With the determination that the 60 mg/kg/day dose group is unreliable, the developmental NOAEL becomes 13 mg/kg/day (LOAEL not established); the fetal data from the 3 and 15 mg/kg/day doses are still considered reliable. The current PODs are below the NOAEL for this study and would therefore be protective of any potential fetal effects at higher dose levels.

Lack of developmental effects was noted in a guideline rat developmental toxicity study up to the highest dose tested (40 mg/kg/day). Specifically, in the rat study, there were no treatment-related increases in fetal deaths/resorptions and there were no treatment-related effects on fetal sex ratios, fetal body weight, or the incidences of fetal runts. There was no evidence of altered fetal ossification rates, dose related malformations, or litter/fetal incidences of any individual structural abnormalities for any treated group.

Based on a WOE approach, HASPOC concludes that a rabbit developmental toxicity study is not needed for fenazaquin at this time. This approach is based on the following: 1) the rabbit appears to be less sensitive than other species; 2) no developmental effects were observed up to 13 mg/kg/day in the existing rabbit (albeit non-guideline) study; 3) no developmental effects were observed up to 40 mg/kg/day in the rat developmental study with no susceptibility observed in the pups; and 4) current PODs are based on a more sensitive species and a new rabbit developmental toxicity study is unlikely to impact the quantitative risk assessment.

d. Acute Neurotoxicity Study

In 2013, the HASPOC indicated that a new ACN study needed to be conducted due to low confidence in the existing acute oral studies due to: 1) deficiencies in the histopathology data in the existing ACN (MRID 48814001); and 2) inconsistent findings in the rat gavage studies. Based on team discussions with the registrant, HASPOC reconsidered the need to conduct a new ACN study.

There is an existing ACN study (MRID 48814001) where the NOAEL is 20 mg/kg bw/day in both genders. The effects noted at the LOAEL included decreased body weight gain and

decreased food consumption at 65/60 mg/kg (M/F). There were no mortalities in the study. The adverse findings at higher doses (120 mg/kg in females, 130 mg/kg in males) included decreased body weight gain, decreased food consumption, mild dehydration, sluggish arousal, unusual posture, abnormal gait/ataxia, abnormal respiration, changes in orienting on auditory reaction, decreased body temperature, neuron vacuolization, decreased motor activity, decreased time in movement. Recently, the TOXSAC reviewed this study and found that it was deficient. Specifically, neuropathology (i.e., nerve fiber degeneration) was observed in the high-dose males, but histopathology at lower doses was not provided As such, a NOAEL was not established for the neuropathology due to incomplete histopathology. Upon further review, HED consulted with ORD, who indicated that the nerve degeneration should not be considered a treatment-related effect at the high dose. HED will be revising the conclusions for the ACN study accordingly.

Inconsistent findings with respect to mortality have been shown in the rat gavage studies where some studies show mortality at doses as low as 30 mg/kg/day after a single dose (immunotoxicity study) while others only show effects, such as changes in body weight or food consumption, at doses ranging from 40-65 mg/kg (ACN, rat developmental study). In the acute lethality study, acute effects of hunched posture, straub tail, hypoactivity, and soft stools were seen at the LOAEL of 50 mg/kg. Also, the oral LD_{50} in the acute lethality study was 134/138 mg/kg (M/F) whereas no mortality was observed in the ACN up to 120/130 mg/kg (M/F). Despite these noted differences in adverse effects noted across the database of rat gavage studies, the NOAELs are similar across studies. Repeating the ACN would not change the findings with respect to the immunotoxicity, acute lethality, and rat developmental studies. Given the conclusions of these other studies and the similar NOAELs across studies, a new ACN is unlikely to impact the acute POD for fenazaquin.

Based on a WOE approach, HASPOC concludes that a new ACN is not needed for fenazaquin at this time. Repeating the ACN study is not likely to add significant new knowledge to the fenazaquin toxicology database or impact risk assessment PODs.

e. Subchronic Neurotoxicity Study

The HASPOC has previously determined that a subchronic neurotoxicity study is needed for fenazaquin. This recommendation was based on clinical signs of hypoactivity and ataxia noted in some oral studies, low levels of fenazaquin detected in the brain (~0.0014% of the administered dose), and the incidence of neuropathology measured in the ACN study at the high dose. The team requested that HASPOC reconsider the need for a subchronic neurotoxicity study.

1. **Evidence for neurotoxicity in the fenazaquin database of toxicology studies:** In an acceptable/non-guideline ACN study, the LOAEL was 65/60 mg/kg/day (M/F) based on decreased body weight gain and decreased food consumption, with a NOAEL of 20 mg/kg/day in both genders. No neurotoxic effects were observed in the ACN study at the LOAEL value of 65/60 mg/kg. There were no deaths observed in this study. At much higher doses, adverse effects included decreased body weight gain, decreased food consumption, mild dehydration, sluggish arousal, unusual posture, abnormal gait/ataxia,

abnormal respiration, changes in orienting on auditory reaction, decreased body temperature, neuron vacuolization, decreased motor activity, decreased time in movement, and muscle/nerve fiber degeneration. In the acute lethality study, acute effects of hunched posture, straub tail, hypoactivity, and soft stools were seen at the LOAEL of 50 mg/kg.

There is no clear evidence of consistent neurotoxicity findings in the other available toxicity studies. Fenazaquin produced decreased body weight and decreased food efficiency in multiple studies of various durations. Excessive salivation was seen in the rat reproduction toxicity study. During premating, the incidence of excessive salivation in the high-dose groups (25 mg/kg/day) was 20/30 F_0 males, 14/30 F_0 females, 21/40 F_1 males, and 16/40 F_1 females (all $p \leq 0.01$). This finding was not seen in control animals and it occurred at low incidence in the low- and mid-dose groups (0-7 animals/group). The incidence of excessive salivation was also significantly increased in high-dose females of both generations during gestation and in high-dose F_0 females during lactation. Increased salivation was also reported in the high dose group of the preliminary one-generation reproduction study in addition to findings of impaired righting reflex (males: 1/10, females: 2/10) and decreased motor activity (females: 2/10) in the high dose group of the preliminary reproduction study. HED considers the excessive salivation endpoint to be well characterized with no residual uncertainty and clear NOAEL/LOAEL values.

2. **Evidence for neurotoxicity in the database of other similar chemicals:** There are no known pesticides with similar structures.

3. **Risk assessment considerations:** The major findings following repeated oral administration in rats, hamsters, and dogs were non-specific effects characterized by decreases in body weight, body weight gain, food intake, and food efficiency. The repeated dosing POD is 5 mg/kg/day based on a LOAEL of 25 mg/kg/day from the rat two-generation toxicity study where excessive salivation and decreased body weight gain and food intake were observed. Similar NOAELs were observed in other repeated dosing studies across multiple species. It is unlikely that a subchronic neurotoxicity study would result in a lower POD.

Based on a WOE approach, HASPOC concludes that a subchronic neurotoxicity study is not needed for fenazaquin at this time. This is based on the following: 1) indications of treatment-related neurotoxicity in the ACN are well-characterized; 2) effects are observed at doses higher than current PODs; and 3) there was no indication of treatment-related neurotoxicity observed in any repeated dosing studies.

IV. HASPOC RECOMMENDATIONS:

Based on a WOE approach considering all the available fenazaquin hazard and exposure information, the following studies **are not required** for fenazaquin at this time: (1) a subchronic inhalation toxicity study; (2) a subchronic dermal toxicity study or a dermal penetration study;

(3) a rabbit developmental toxicity study; (4) an ACN study; and (5) a subchronic neurotoxicity study.

In determining the need for a subchronic inhalation study, EPA's WOE decision process included both hazard and exposure considerations as well as incorporation of a presumed 10X database uncertainty factor (UF_{DB}) for the lack of this study. Thus, the agency's LOC in the HASPOC's WOE evaluation for inhalation exposure risk assessment is a MOE of 1,000 which includes the 10X inter-species extrapolation, 10X intra-species variation, and the 10X UF_{DB}. In the case of fenazaquin, all residential (MOEs = 380,000 to 3,000,000) and occupational (MOEs = 1,100 to 220,000) handler inhalation MOEs were higher than the LOC of 1,000 when using an oral POD. This indicates that the lack of an inhalation study does not reduce the overall confidence in the risk assessment or result in an uncertainty (i.e., the study will not provide a POD sufficiently low to result in a risk of concern).